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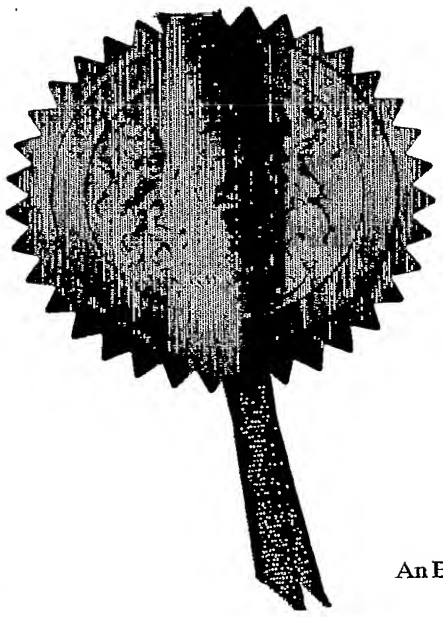

Signed Stephen Hordley

Dated 22 February 2005

Patents Form 1/77

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6 FEB 2004

The Patent Office
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1. Your reference

GDM-MP100106-GB

2. Patent application number
(The Patent Office will fill this part in)

0402736.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Tayside Flow Technologies Limited
Unit 20, Prospect Business Centre
Gemini Crescent,
Dundee Technology Park
Dundee DD2 1TY

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

UK 07979933002

4. Title of the invention

A Drug Delivery Device

5. Name of your agent *(if you have one)*

Lloyd Wise, McNeight & Lawrence
Highbank House
Exchange Street
STOCKPORT
Cheshire
SK3 0ET

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

08458275001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Yes

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	9
Claim(s)	2
Abstract	1
Drawing(s)	2 x 2 = 4

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) [signature] Date 05/02/2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

Mr G D McCallum 0161 480 6394

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A DRUG DELIVERY DEVICE

The present invention relates to a drug delivery device and, more particularly, an implantable drug delivery device.

It is known in the art to implant intravascular stents into the blood vessels of individuals where there has been stenosis of the blood vessel. Typically, the stent comprises an expandable tube which is introduced into the individual remote from the site of stenosis. The stent is moved into position in the blood vessel of the individual and then, once in place, expanded so as to enlarge the blood vessel and so restore normal blood flow.

WO00/38591, PCT/GB02/05276 and PCT/GB02/05234 (each of which is incorporated herein by reference) disclose that an intravascular stent may be provided with a helical formation in its interior so as to induce helical or spiral blood flow in the blood vessel in which it is implanted. The helical formation can be a ridge or a groove. The benefit of introducing helical or spiral blood flow is that turbulent flow and dead regions (which can be a problem in stents without a helical formation) can be eliminated. This, in turn, reduces the likelihood of plaque formation, reduced flow capacity and thromboses in the blood vessel.

Similarly, it is known to implant vascular grafts into a blood vessel to replace a damaged section of blood vessel.

It is often the case that individuals who require the implantation of a stent or graft also require the administration of one or more drugs. Usually this will be due to the implantation of the stent or graft, itself, such as the need to administer a drug to prevent restenosis or to reduce the risk of a thrombus forming in the stent or graft after implantation. However, in some instances, a drug may have to be administered for entirely separate reasons.

It is known in the art to deliver drugs into the blood stream of an individual by introducing the drug into an implant itself, in such a way so as to allow the drug to be steadily released from the implant. This is particularly advantageous if the drug is to be delivered to the area immediately surrounding the implant, for example if the drug is to prevent restenosis. However, the problem with such arrangements is that the surface area of a stent or graft that is actually in contact with the blood of an individual is, in fact, relatively small and because of this the stent or graft has a low drug carrying ability. This is both

with respect to the absolute amount of drug that can be carried by the stent and with respect to the rate at which the drug can be delivered to the blood stream of the individual.

Accordingly, the present invention seeks to alleviate one or more of the above problems.

According to the present invention, there is provided a drug delivery device comprising: a drug; and a vascular implant having a blood-contacting surface and a helical formation on the blood contacting surface, the drug being releasably associated with the helical formation of the vascular implant. Such a drug delivery device has an improved drug carrying and drug delivery ability because of the increased surface area provided by the helical formation.

Conveniently, the drug is mixed into the material from which the helical formation is made.

Alternatively, the drug is coated onto the surface of the helical formation.

Preferably, the helical formation is made from a polymer, preferably a polymer foam, more preferably polyamide, polyester or polyurethane.

Advantageously, the drug is bound onto the cellular structure of the polymer.

Conveniently, the drug is an anticoagulant, an antiplatelet agent, an angiogenesis inhibitor; a cyclo-oxygenase inhibitor; a gene therapy agent or a mixture of two or more of said drugs.

Preferably, the vascular implant is an intravascular stent, an intravascular stent insert or a vascular graft.

Advantageously, the vascular implant is a stent and the drug delivery device further comprises a sleeve positioned surrounding and/or within the stent.

Conveniently, the sleeve is made from expanded PTFE.

Preferably, the drug is also releasably associated with the blood-contacting surface of the vascular implant.

Advantageously, one or more further drugs are provided releasably associated with the helical formation and/or the blood-contacting surface of the vascular implant.

The terms "helix", "helical" and "spiral" as used herein cover the mathematical definition of helix and helical and any combination of mathematical definitions of helical and spiral.

In order that the present invention may be more readily understood and so that further features thereof may be appreciated, embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings in which:-

Figure 1 is a perspective view of a drug delivery device in accordance with one embodiment of the present invention; and

Figure 2 is a perspective view of a drug delivery device, having a stent insert, in accordance with another embodiment of the present invention, in a compressed condition;

Figure 3 is a perspective view of the drug delivery device of Figure 2, in an expanded condition;

Figure 4 is a perspective view of the stent insert of the drug delivery device of Figure 2; and

Figure 5 is a magnified view of one end of the stent insert of Figure 4.

Referring to Figure 1, a drug delivery device 1 comprises a tubular vascular graft 2 into the exterior of which a groove 3 has been pressed. The groove 3 has been pressed in a helical form such that a corresponding helical ridge 4 runs along the length of the interior of the graft 2. Thus the helical ridge 4 forms a helical formation on the graft 2.

In this embodiment, the graft 2 is made from a woven or knitted polymer such as polyamide or polyester. However, the graft could be manufactured from other materials such as polyurethane or expanded polytetrafluoroethane (ePTFE). The graft could also be manufactured from a combination of any of these materials. It is not essential that the graft 2 be made from a polymer, however, and in other embodiments it is made from a ceramic.

In some embodiments, the graft 2 is also coated with a biocompatible material such as a polyurethane. It is preferred that such coatings are polymer coatings which mimic the chemistry of the human body. Most preferred are coatings which are hydrophobic as this

provides adhesion and stability. In some embodiments the polymer coatings are crosslinked, which increases their robustness, and in certain embodiments, the coatings are positively or negatively charged.

Mixed into the graft 2 or the coating is an anticoagulant drug such as heparin. In this embodiment, the polymer which forms the graft 2 and the ridge 4 includes the anticoagulant drug. However, in other embodiments, only the polymer which forms the ridge 4 includes the drug.

In use, the graft 2 is implanted into a blood vessel of an individual as is known in the art. Thus a blood vessel of the individual abuts and is attached to either end of the graft 2 (e.g. using sutures) and the blood of the individual flows through the interior of the graft 2. Accordingly, the interior of the graft 2 and the ridge 4 form a blood-contacting surface of the drug delivery device 1. The helical ridge 4 induces a helical spiral flow to the blood.

The anticoagulant drug is mixed into the polymer that forms the graft 2 such that, upon implantation of the graft 2, the drug diffuses from the graft 2 and, in particular, from the ridge 4 into the blood and thus is released into the blood stream of the individual. In some embodiments, the drug is mixed into the polymer so as to be released at a particular time. In other embodiments, the drug is released steadily over a prolonged period of time. The anticoagulant drug lowers the ability of the blood to coagulate and thus reduces the likelihood of a thrombus forming.

It is to be appreciated that the ridge 4 has a considerable surface area in contact with the blood because of its cross-sectional shape. The significant amount of blood which comes into contact with the ridge 4 as it passes through the graft 2 results in the rate of transfer of the drug into the bloodstream being relatively high. Furthermore, a greater quantity of the drug is held adjacent the surface of the graft 2, due to the ridge 4, than is possible with a graft of the same size lacking a helical ridge. Therefore the ridge 4 provides improved drug carrying ability.

In alternative embodiments, the drug is not an anticoagulant drug. For example, in some embodiments, the drug is instead one of the following drugs: an antiplatelet agent; an angiogenesis inhibitor; a cyclo-oxygenase inhibitor; or a gene therapy agent. In further embodiments of the present invention, a mixture of two or more of these drugs is provided.

In the above described embodiment of the present invention, a ridge is provided on the interior of the graft 2. It is to be appreciated that, in other embodiments of the invention, a plurality of helical ridges are provided along the interior of the graft 2, preferably equally spaced about the axis of the graft 2. Furthermore, in alternative embodiments, the ridge is replaced or supplemented with one or more helical grooves on the interior surface of the graft. Each groove works in much the same way as the ridge, causing the blood flow to be helical or spiral. Furthermore, when the graft is implanted, the groove increases the surface area of the graft in contact with blood and thus improves the drug carrying ability of the drug delivery device. Thus the grafts include a helical formation which is either one or more ridges, one or more grooves or a combination of both.

Referring to Figure 2, a further drug delivery device 5 is shown. The drug delivery device 5 comprises a wire mesh intravascular stent 6 which is in the form of a compressed tube. Attached to the interior surface of the wire mesh stent 6 is a stent insert 7 made from a polymer foam such as polyurethane. However, it is not essential that the stent be made from a polymer and, in some embodiments, it is, for example made from a ceramic. The insert 7 is elongate, having a broad base 8 and a centrally disposed perpendicular fin 9 such that the stent insert 7 has a bell-shaped cross-section. The insert 7 is attached to the wire mesh stent 6 so that it follows a helical path, about the axis of the stent 6. Thus the insert 7 is a helical formation. A drug is mixed into the polymer foam of the insert 7. In alternative embodiments, the drug is coated onto the surface of the insert 7, again, as described in previous embodiments.

In use, the stent 6 is implanted into a blood vessel of an individual in the usual way. The stent 6 is introduced into a blood vessel of an individual in its compressed form, as is shown in Figure 2. When it is correctly positioned, the stent 6 is opened out into its expanded form as is shown in Figure 3. Thus, a blood vessel of the individual surrounds the stent 6 and the blood of the individual flows through the interior of the stent 6. Accordingly the stent 6 and the insert 7 are in contact with the blood of the individual and the insert 7 imparts a helical flow to the blood. The insert 7 has a considerable surface area in contact with the blood of the individual because of its bell-shaped cross-section and the drug is readily released from the insert 7 (as denoted by the arrow 10 in Figure 5). Thus the stent insert 7 has a high drug carrying ability, both in terms of the rate at which the drug can be released into the blood and in terms of the absolute amount of drug that is stored adjacent the surface of the insert 7.

In further embodiments of the present invention, the stent insert 7 and the stent 6 form a single, integral stent having a helical formation. In some of these embodiments, the helical formation has a differently shaped cross-section such as a square-shaped or U-shaped cross-section rather than a bell-shaped cross-section. In some of these embodiments, the drug is mixed into or coated on the helical formation, alone, but in other embodiments, the stent, as a whole, is made from or coated in a polymer material in which the drug is mixed or on which the drug is coated. Thus, in these embodiments, the drug is released not only from the helical formation but from the stent, itself.

It is to be appreciated that, in some embodiments, a different drug is mixed into or coated on to the helical formation from that which is mixed into or coated on to the stent, itself. Therefore, these embodiments permit the release of two separate drugs simultaneously. Moreover, the two drugs may be released in different concentrations or over different time periods. It is also to be noted that in some embodiments, the helical formation has more than one drug releasably associated with it.

In variants of these embodiments, one or more helical formations (either ridges or grooves) are provided about the interior of the stent, preferably equally spaced about the axis of the stent.

In these embodiments, because of the helical formations on the interior of the stent, the stent has increased surface area in contact with the blood of the individual which results in the stent having an improved drug carrying ability. Furthermore, the provision of the helical formations on the interior of the stent means that, in embodiments where the drug is provided, mixed into or coated onto only the helical formations, the drug does not come into direct contact with the blood vessel or other organ into which the stent is implanted. Thus the drug is only exposed directly to the flow of blood (or other fluid). This can avoid the delivery of the drug being too concentrated in bodily regions that directly contact the stent. It is also to be noted that the provision of the drug mixed into or coated onto the helical formation gives better release of the drug because the helical formations are positioned more in the flow of the blood than the stent is itself.

In some other embodiments of the present invention, the wire mesh intravascular stent 6 is provided with a sleeve made, for example, from expanded PTFE, that surrounds, or sits inside, the stent, itself. In some of these embodiments, one sleeve is provided around the stent 6 and another sleeve is provided within the stent 6. The effect of the sleeve is to

cushion the blood vessel or other surrounding organ of the individual (if the sleeve surrounds the stent 6) or to protect the bloodstream or other fluid from the wire stent 6 (if the sleeve is provided within the stent 6). Where a sleeve is provided within the stent 6, the sleeve, itself, may have the drug mixed in with it, or coated on it, in order to be released as has been described in previous embodiments. Furthermore, in certain embodiments, the insert 7 is integral with the inner sleeve.

Accordingly, it is to be appreciated that the present invention may be implemented with a range of vascular implants having helical formations of which vascular grafts, intravascular stents and stent implants have been described as detailed embodiments herein.

The advantages that may be achieved by embodiments of the present invention are a reduction in the thickness of the neointimal layer and a decrease in the neointimal area; a reduction in the potential for inflammation; an improvement in the performance (of the delivery of the drug and in blood flow) downstream of the device: the provision of a broad therapeutic window; provision of an environment allowing normal re-endothelialisation and an increase in pharmacokinetics (i.e. an increase in the delivery of a drug when and where it is required).

The processes by which a drug is releasably associated with the vascular implant or its coating will now be described in greater detail.

It is firstly to be understood that there are several different ways that a drug may be releasably associated with the implant. For example, the association of the drug with the vascular implant may be selected from: a drug solution coating; a drug reservoir system with a porous polymer coating or nanoporous ceramic covering; a degradable drug and polymer combination; and a cell membrane lipid bi-layer coating selected from phosphoryl chlorine, phosphoryl ethanolamine or phosphoryl serine. If the vascular implant is a stent then, in some embodiments, the stent is itself, degradable.

There are also several different methods by which the drug can be mixed into the vascular implant, itself, or into its coating, depending upon the material from which the vascular implant or coating is made. If the drug is to be mixed into the vascular implant, itself, then this can be done using a drug/polymer mixed solution, to bind the drug into the polymer; or by vacuum loading of the drug into a porous polymer or ceramic.

Alternatively, the drug can be mixed into a polymer that forms the vascular implant by encapsulating it in the polymer. In order to do this, "micro-beads" can be used. In these embodiments, a bead is provided having a large number of channels so that it takes on the form of a sponge. The drug is attached to surfaces on the outside and within the bead, by the drug entering the channels. Nevertheless, the polymer forming the vascular implant is not necessarily a foam and is, for example, in some embodiments polyurethane or another polymer within which the drug is fixed into the microstructure, for release.

In a variation of this embodiment, instead of the drug being mixed into the polymer that forms the vascular implant, the drug is coated onto the interior surface of the vascular implant, in particular the helical formation. In preferred embodiments, the drug is coated by binding it into the cellular structure of the polymer. However, even in this variant, the effect is the same, namely that, when the vascular implant is implanted, the drug is released from the vascular implant, in particular from the helical formation, and into the blood stream of the individual.

If the drug is in the coating of the vascular implant then one method of achieving this is drip a solution of the polymer coating and drug solution onto the vascular implant. Alternatively, and particularly for temperature-sensitive drugs, the coating, containing the drug, can be cold moulded onto the vascular implant. Another possibility is to pressure mould the coating onto the vascular implant. A further possibility is to coat the vascular implant in two steps. In the first step, an absorbent polymer or ceramic coating is applied to the vascular implant and in the second step, a drug solution is applied to the coating.

It is to be understood that these methods of incorporating drugs into an implant or coating the drug onto an implant are known in the art. As examples of known products which have a drug releasably associated with them, reference may be made to the following table.

Manufacturer	**Drug**	**Coating**
Cordis™	Rapamune™	Surmodics ™ Coating Process
Boston Scientific ™	Paclitaxel	Polymer based delivery system

Guidant ™	Everolimus (Analogue of Rapamycin)	Resorbable polymer formulation
Guidant™	Everolimus (Analogue of Rapamycin)	Two coat polymer
Guidant ™ Cook	Paclitaxel	Polymer free coating
Medtronic ™ Abbott Laboratories ™	ABT-578 Rapamycin	P.C. (phosphorylcholine)
Jomed™	Tacrolimus	Nanoporous ceramic
Vascular Architect™	Nitric-oxide Generator	PTFE coating
Cardiotech International ™	Rapamycin	Chronoflex Polyurethane
Terumo™	Angio Tensin 2 Receptor	Polyactic Acid Layer

Claims

1. A drug delivery device comprising: a drug; and a vascular implant having a blood-contacting surface and a helical formation on the blood contacting surface, the drug being releasably associated with the helical formation of the vascular implant.

2. A drug delivery device according to claim 1 wherein the drug is mixed into the material from which the helical formation is made.

3. A drug delivery device according to claim 1 wherein the drug is coated onto the surface of the helical formation.

4. A drug delivery device according to any one of the preceding claims wherein the helical formation is made from a polymer, preferably a polymer foam, more preferably polyamide, polyester or polyurethane.

5. A drug delivery device according to claim 4 as dependent on claim 3 wherein the drug is bound onto the cellular structure of the polymer.

6. A drug delivery device according to any one of the preceding claims wherein the drug is an anticoagulant, an antiplatelet agent, an angiogenesis inhibitor; a cyclo-oxygenase inhibitor; a gene therapy agent or a mixture of two or more of said drugs.

7. A drug delivery device according to any one of the preceding claims wherein the vascular implant is an intravascular stent, an intravascular stent insert or a vascular graft.

8. A drug delivery device according to claim 7 wherein the vascular implant is a stent and the drug delivery device further comprises a sleeve positioned surrounding and/or within the stent.

9. A drug delivery device according to claim 8 wherein the sleeve is made from expanded PTFE.

10. A drug delivery device according to any one of the preceding claims wherein the drug is also releasably associated with the blood-contacting surface of the vascular implant.

11. A drug delivery device according to any one of the preceding claims wherein one or more further drugs are provided releasably associated with the helical formation and/or the blood-contacting surface of the vascular implant.

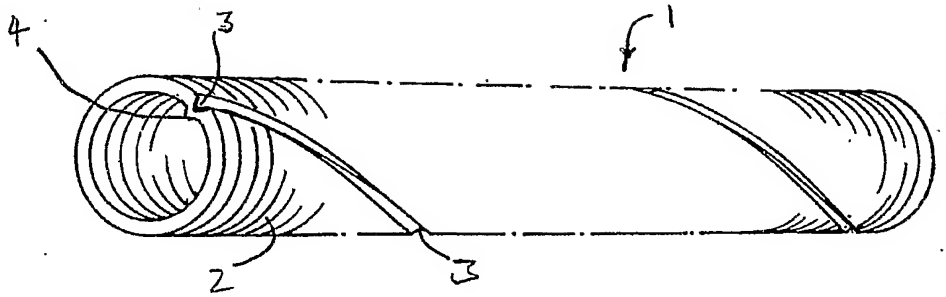
12. A drug delivery device substantially as herein described with reference to and as shown in the drawings.

ABSTRACT

A DRUG DELIVERY DEVICE

A drug delivery device is disclosed. The device comprises a vascular implant having a helical formation. A drug is releasably associated with the helical formation.

FIG. 1



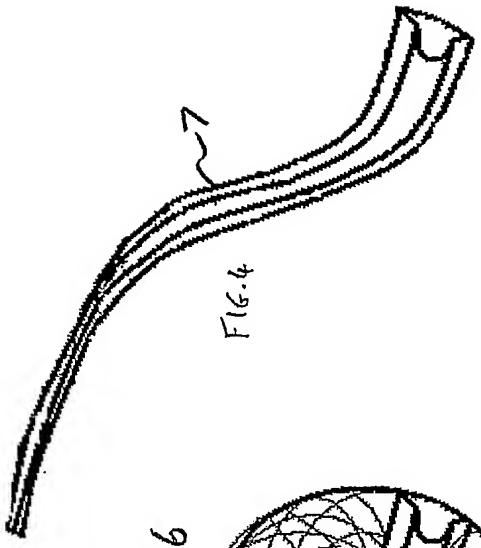


FIG.4

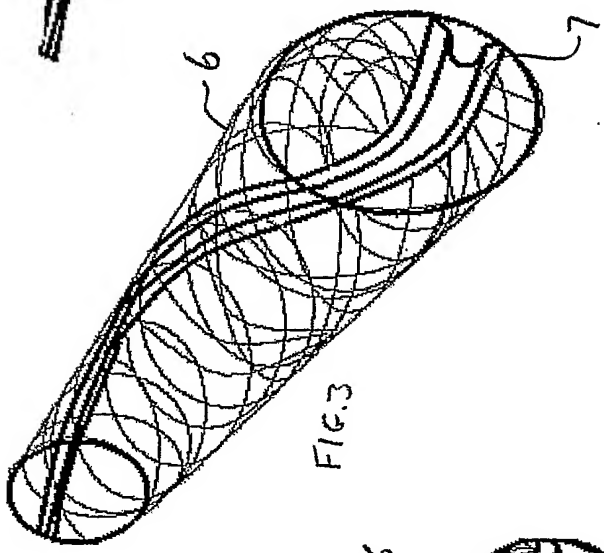


FIG.3

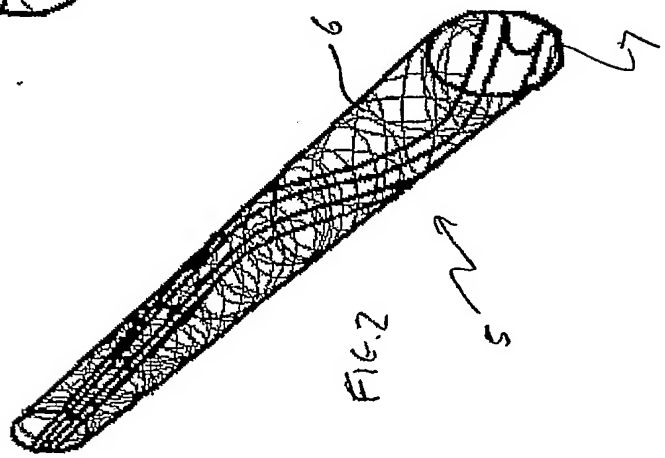


FIG.2

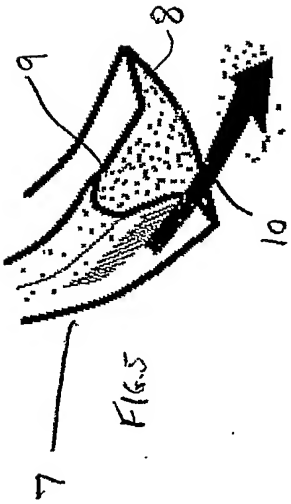


FIG.5